REMARKS/ARGUMENTS

New claim 39 corresponds to subject-matter of claim 18 filed on June 6, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0025], [0026], [0028], [0075], [0081], [0044] and reference number 13 in Figs. 1-5, 7 of the published version of the present application.

The new claim 39 has also been clarified in that it relates to a method of producing pre-metered dry powder combined dose. This is evident to the person skilled in the art when reading the active steps of the claim 39 as these steps are performed, e.g., by a dose/dose product manufacturer and are separate from the actual inhalation and treatment procedure. This amendment is further supported in the application as filed, especially in paragraphs [0022], [0071], [0072].

New claims 40-45 and 47 correspond to subject-matter of claims 19-24 and 26 filed on June 6, 2006.

New claim 46 corresponds to subject-matter of claims 25 and 37 filed on June 6, 2006.

New claim 48 corresponds to subject-matter disclosed in the application as filed, especially in paragraphs [0075]. This paragraph discloses that the foil is preferably designed to be opened by a foil cutting arrangement, which is further evident from careful investigation of the foils in Figs. 1-5, 7. In these figures it is evident that, for example, it is not possible to open the foil through e.g. a peelable action since the foil is fixed to the common dose bed in such a way that it cannot be peeled therefrom.

New claim 49 corresponds to subject-matter of claims 18, 27 filed on June 6, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0025], [0026], [0028], [0075], [0081], [0044] and reference number 13 in Figs. 1-5, 7 of the published application.

The new claim 49 has also been clarified in that it relates to a pharmaceutical dry powder combined dose product. This amendment is further supported in the application as filed, especially in paragraphs [0071] and [0072].

New claims 50-59 correspond to subject-matter of claims 28-38 filed on June 6, 2006.

New claim 60 corresponds to subject-matter disclosed in the application as filed, especially in paragraph [0075]. In this paragraph it is disclosed that the seal formed by the protective foil is opened to allow access to the combined dose on the dose bed. The at least one protective foil is designed to be opened by a foil cutting arrangement, which is further evident from careful investigation of the foils in Figs. 1-5, 7. In these figures it is evident that, for

example, it is not possible to open the foil through e.g. a peelable action since the foil is fixed to the common dose bed in such a way that it cannot be peeled therefrom.

No new matter has been entered.

The objection to the claims 18-38 under 35 U.S.C. 112, first and second paragraphs, are no longer relevant to the new claims 39-60.

In the Office communication the following prior art documents were cited:

Gavin	WO 01/78737 A1
Haikarainen et al.	WO 00/64519 A1
Trofast	US 6,030,604

Gavin concerns a pharmaceutical formulation that constitutes a combination of (R,R,)-formoterol and budesonide for use in medicine and especially in the prophylaxis and treatment of respiratory diseases (page 1, lines 3-7, 29-33; page 3, lines 5-15). The formulation may also include a pharmaceutically acceptable carrier/excipient and at least one more therapeutic ingredient (page 2, lines 11-12; page 5, line 31-page 6, line 4). The two active agents can be administered simultaneously or sequentially (page 2, lines 1-3; page 5, lines 1-3, 12-16).

When administered simultaneously, the two active agents are provided as a **mixture** (page 7, lines 5-8; Example 1-4) in, for example, a single patient pack (page 5, lines 12-14; page 6, lines 12-14; page 7, lines 5-8). In the case of sequential delivery, each active agent is provided in a separate patient pack (page 5, lines 12-14) and there will be a delay between the two administration occasions (page 2, lines 3-5). For example, two separate actuations can be used to deliver the therapeutically effective combination of the two agents in the case of a pressurized aerosol (page 7, lines 22-24).

As a consequence, the product of Gavin to be used for simultaneous administration uses a **mixture** or **blend** of the two active agents. This embodiment therefore does not teach a separate depositing of the two active agents onto a common dose bed.

Furthermore, the product of Gavin to be used for sequential administration consists of two **separate** products (capsules, cartridges, blisters) and does not present any common dose bed. Such a solution is also **not** designed to deliver the two active agents during the course of a **single** inhalation. In clear contrast, this embodiment of Gavin is actually incompatible with complete delivery at a single inhalation occasion.

In all examples presented by Gavin relating to dry powder formulations, the (R,R)-formoterol fumarate and budesonide active ingredients are micronized and bulk **blended** with the lactose excipient. The resulting **blend** can then be filled in hard gelatin capsules, cartridges or double foil blister packs (page 8, line 17-page 9, line 15).

Gavin therefore does not teach or even suggest a separate depositing of a bronchodilating medicament and an anti-inflammatory medicament onto a common dose bed and where the resulting combined dose on the dose bed is designed to be delivered during the course of a single inhalation.

Haikarainen discloses a multi-dose dry powder inhaler (DPI), wherein the inhaler comprises two medicament containers, each containing a supply of dry medicament powder corresponding to a multitude of metered doses (page 3, lines 21–23). In connection with an inhalation, medicament powder from the two containers is transferred to a metering member equipped with two dosing recesses for receiving a metered dose of the respective powdered medicament (page 3, lines 23-25). The inhaler then has two aerosolization channels, each positioned over one of the two recesses (page 2, lines 29-31, page 4, lines 29-31). The metered doses are discharged simultaneously through the different aerosolization channels and are mixed first in the mouth piece or, if employing separate aerosoloziation channels, in the user's air channel or respiratory tract (page 2, lines 27-29; page 4, lines 34-37).

Haikarainen also teaches a method for inhalation using the described multi-dose dry powder inhaler. The method involves metering a dose of a first and a second powder medicament simultaneously from the respective supplies in the dry powder inhaler (page 3, lines 30-34). Thereafter the metered dose of the first medicament and the metered dose of the second medicament are brought simultaneously into the air flow path of the inhaler through separate flow paths (page 3, lines 34-37). The two doses are then inhaled through the inhaler and become mixed first at the air channel/respiratory tract of the inhaling patient (page 2, lines 28-29; page 3, lines 37-39).

In the issued Office action, the Examiner states that the metered two powder medicaments are delivered from the dosing recess to <u>one position</u> and then inhaled as a combined dose. The only position within the inhaler device of Haikarainen where the two metered powder medicaments become transferred to is the mouth piece of the inhaler device during an inhalation action. The applicant respectfully disagrees that the person skilled in the art would consider this as a separate deposition of two metered medicaments onto a common dose bed. In the present technical field, the term "dose bed" denotes an area onto which

medical powder is deposited during a dose forming process. As a consequence, a surface with which metered powder may collide as the powder is transported by an inhalation air stream during inhalation hardly qualifies as a dose bed as used in the art.

In addition, the new claims specify that the pre-metered formulates are separately *deposited* onto a target area of the dose bed. The definition of this term "deposit" in Merriam-Webster's Collegiate® Dictionary is "to place for safekeeping". Thus, to deposit powder on a dose bed implies placing the powder on the dose bed, where the powder is kept until use in form of inhalation. The extremely short collision between powder and a mouth piece during inhalation does not qualify as "deposition" as defined and understood within the art.

Similar argumentation is also relevant for the dose recesses of Haikarainen. These two separate recesses do not qualify as a common dose bed as defined in the art and in the present invention. However, as is evident from the discussion below, the new claims are still novel and inventive over Haikarainen irrespective of whether Haikarainen actually discloses separate depositing of pre-metered powder onto a dose bed.

Haikarainen never teaches the sealing of the combined dose on the dose bed with a protective foil. In clear contrast, with the Examiner's definition of the dose bed in Haikarainen, the powder will, directly after colliding with the inner mouth piece surface, be transported by the inhalation air stream into the user's mouth and respiratory tract.

Correspondingly, the metered doses in the dose recesses are never sealed by any protective foil to prevent the doses from ingress of moisture. In clear contrast, sealing of the recesses is not functionally possible within the multi-dose DPI of Haikarainen. This further points to the fundamental differences between Haikarainen and the present invention. In Haikarainen, a dose comprising multiple medicaments is metered in connection with an inhalation occasion and this metering is performed inside the DPI. The present invention teaches provision of medical products and pre-metered combined doses that are generated separate from the DPI and delivered as a physical entity that can be inserted into the DPI, where the sealed powder will be delivered.

Furthermore, Haikarainen never teaches that any sealed combined dose is designed for insertion into a DPI, where the combined dose becomes inhaled during the course of a single inhalation. In clear contrast, the combined dose of Haikarainen is produced inside the multi-dose DPI. This should be compared to the present invention as defined by new claims, where the combined dose is generated and sealed outside of and separate from the DPI and will then be inserted into the DPI in connection with an inhalation.

As a consequence, the present invention as defined by the new claims is clearly novel over Haikarainen. In addition, the teachings of Haikarainen cannot be modified in any obvious way to render the present invention obvious. For example, no sealing of the powder colliding with the mouth piece in Haikarainen is possible using a protective foil since the powder is actually carried by the inhalation air stream and if any sealing would be possible no powder will of course be delivered to the user. There are further no evident modifications of Haikarainen's DPI that would result in a sealed combined dose that can be inserted into the DPI.

Furthermore, Haikarainen is marred by several disadvantages in the form of gradient formation in the powder store of the inhaler and moisture leakage into the store. Those familiar with the field of powder technology are well aware that powder containing a range of particle sizes, whether it is a perfect, ordered mixture or a single dry powder formulation, runs a risk of having small particles segregate from larger ones when the powder is being transported or handled in a metering process. For instance, small particles tend to fall to the bottom of a store by gravitation, so that over time the concentration of small active particles increases near the bottom of the store leading to depletion at the top of the store. A consequence of this is that the fine particle dose of active agent in the metered doses will drift from too much to too little, or vice versa depending on the metering process, during the run of a metering process, although the metered dose mass is reasonably constant over the inhaler use time. As a result, the inhaled active dosage will vary considerably depending on whether the dose was produced early or late in a use time of the inhaler. This is not acceptable, of course.

In addition, by having a store of powder in the multi-dose DPI of Haikarainen, moisture will migrate into the powder and thereby cause the powder particles to agglomerate and aggregate into larger clusters, which in turn affects the gradient and size distribution discussed above, and makes it very hard to deliver fine particles at the desired location in the user's respiratory system. See for example, Keller et al. (U.S. Patent Application No. 10/628,965 and published under number 2004/0202616 A19) where Keller discusses the moisture problems that are inherent in multi-dose DPI (paragraph [0007], [0016]).

In Haikarainen, each dose is metered and generated inside the DPI. This means that the dose metering can take place in a high temperature and high moisture environment, depending on the current ambient conditions. The DPI of Haikarainen is also dependent on a movable recess that transports powder from a store chamber to an inhalation situation. As the

person skilled in the art is well aware of, it is next to impossible to have completely moisture-tight DPIs with such movable parts. This should be compared to the present invention, where the powders are separately metered and deposited onto a dose bed and sealed in a controlled environment and not the user environment as Haikarainen.

Not even by combining the teachings of Gavin and Haikarainen would the person skilled in the art arrive at something falling within the scope of the present invention. As Gavin is mostly directed to production of a formulation that can be used for treating a respiratory disorder, this formulation could be used by the skilled person for delivery by multi-dose DPI of Haikarainen.

In such a case, the skilled person could fill the first multi-dose bulk container with (R,R,)-formoterol and the other bulk container with budesonide. The two active agents will then be metered separately at the two dosing recesses but will never be separately deposited onto a common dose bed for the reasons described in the foregoing. In addition, no sealing of the doses by at least one protective foil will be possible inside the multi-dose DPI.

In an alternative approach, the skilled person could fill a first bulk container with a mixture of (R,R,)-formoterol and budesonide and fill the other bulk container with the same powder mixture or a third pharmaceutically active ingredient. However, in such a case the formoterol and budesonide powders are not separately metered and separately deposited onto a common dose bed but indeed provided as a mixture. No sealing of the doses with a protective foil is possible in this approach.

Trofast teaches a dry powder composition comprising one or more pharmaceutically active substances and a carrier substance, which all are in finely divided form and the resulting formulation has a pored bulk density of from 0.28 to 0.38 g/ml (column 1, lines 26-32). Trofast teaches that a combination of budesonide and formoterol can be employed (column 2, lines 11-12; column 4, lines 31-54). However, Trofast teaches that all the ingredients, i.e. the active substance(s) and the carrier substance, are **mixed** to form a uniform mixture (column 3, lines 37-39, 64-67; column 4, lines 16-18, 39-41; claims 4, 6, 8, 11).

Trofast does therefore not teach a separate depositing of pre-metered medicaments onto a common dose bed nor any sealing of the combined dose on the dose bed with at least one protective foil.

Trofast does not provide the skilled person with any further teachings besides the combination of Gavin and Haikarainen. As a consequence, the skilled person would never

arrive at something falling within the scope of the new claims even with a combination of Trofast, Gavin and Hairkarainen.

Accordingly, and because none of the reference either alone or in combination disclose or suggest the subject matter of the newly presented claims, Applicants respectfully request the reconsideration and withdrawal of the outstanding rejections.

Respectfully submitted,

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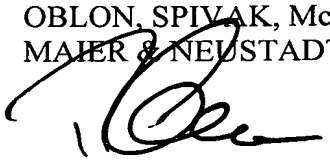

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